temozolomide (TMZ) being "administered p.o. at doses ranging from 50 mg/m^2/day to 250 mg/m^2/day for 5 days, every 4 wks." (lines 8 and 9 of abstract). The Examiner notes that the Nicholson et al. reference teaches administering TMZ "orally for 5 days, with subsequent courses administered every 21 to 28 days. . . . Dose levels tested included 100, 150, 180, 215, 245 and 260 mg/m^2 daily" (lines 5-7 of abstracts). The Examiner also notes that the reference(s) do not teach all the steps in the claims, including the rest period of 5-14 days. The Examiner concludes that one skilled in this art would be motivated to modify the resting period and closing period in the absence of a side-by-side comparison.

Per Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) and MPEP § 2144, the criteria for a prima facie case of obviousness are:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence in the application indicating obviousness or nonobviousness.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention

is rendered obvious....'[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" In re Fritch, 23 U.S.P.Q.2d at 1784 (quoting In re Fine, 5 U.S.P.Q.2d at 1600).

Applicant respectfully traverses the rejection and presents the following comments. Because of the differences between the scope of the prior art and the claimed invention, per the first and second Graham factors, applicant respectfully suggests that a prima facie case of obviousness cannot be established.

The scope and contents of Dhodapkar are as follows. The Dhodapkar article describes the toxicity, pharmacokinetics and anti-tumor activity of TMZ administered on an oral 5-day schedule to patients with or without prior exposure to nitrosurea (NU). Similar to methods prior to the present invention, the Dhodapkar administers doses over a 28-day cycle in which TMZ is administered daily for the first five days of the cycle followed by 23 days of the rest, in which it is not administered. See also, Newlands et al., Br. J. Cancer 65(2) 287-291 (1992). Further, the Dhodapkar article discloses that 50 mg/m^2/day to 250 mg/m^2/day for 5 days of TMZ is administered.

The scope and contents of Nicholson are as follows. The Nicholson article describes a phase I trial of TMZ with or without prior craniospinal irradiation. Nicholson is limited to a TMZ dose schedule similar to that of Dhodapkar and other generally accepted methods, i.e. 5 days of dosing at 100 to 260 mg/m^2/day for 5 days, followed by 21 to 28 days of rest.

Applicant claims a dosing of TMZ for at least two cycles, wherein each cycle comprises a dosing period of at least five days at a dose level of 40 to 150 mg/m^2/day, followed by a rest period of 5 to 14 days in which TMZ is not administered.

Applicant's invention differs from the prior art in that the rest period of applicant's claim 1 is 5 –14 days, well below the rest period taught by the Dhodapkar and Nicholson articles. Additionally, the **maximum** dosing range of claim 1 is 150 mg/m^2/day, a **maximum** dose level well below that of the maximum dose levels of the Dhodapkar and Nicholson articles. The present invention's nonobviousness resides in its shorter rest periods and generally lower dose levels. The longer rest periods and significantly higher maximum dose levels of both Dhodapkar and Nicholson teach away from the shorter rest period and lower **maximum** dose of the present invention. Further, the present invention is not specifically limited to cancer treatments requiring pre-treatment with nitrosurea or prior cranio-spinal irradiation treatment combined with TMZ, as described by Dhodapkar and Nicholson,

respectively. The Examiner has acknowledged that Dhodapkar and Nicholson do not teach all the steps in the claims, including the rest period of 5-14 days. Nowhere in either Dhodapkar or Nicholson is there any suggestion of the lower resting periods or the decreased **maximum** dosage level of the present invention. Applicant further points out that its cyclical dosing schedule is not limited to 5 days, unlike Dhodapkar and Nicholson. Applicant submits that the present invention is not obvious over the methods disclosed in Dhodapkar, Nicholson or combination thereof.

With regard to the Examiner's comments regarding motivation to modify the resting period in the absence of a side-by-side comparison, applicant respectfully submits the following. There is no suggestion or motivation in the art that following the methods of Dhodapkar and Nicholson would lead one of ordinary skill in the art to pursue the method of claims 1-11. There is no suggestion in either article that would motivate one of ordinary skill in the art to use a shorter rest period with the present invention's lower **maximum** TMZ dosage level and potentially longer cyclical dosing period. As discussed above, the different (i.e. longer) rest and cyclical dosing periods and higher maximum dose amounts of Dhodapkar and Nicholson would not motivate one of ordinary skill in the art to pursue the claimed invention. Applicant submits that this ground of rejection should be withdrawn.

Claims 12-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the CA 2,184,545 (CA '545) patent. The Examiner notes that CA 2,184,545 teaches a capsule containing 5 mg of temozolomide (See Abstracts last three lines). The Examiner states that the claims are directed to a kit containing a 5-mg unit dose form of temozolomide and a pharmaceutical acceptable carrier. The Examiner states that accordingly, one of skill in art would be motivated to use the prior art unit dosage form in a kit. The Examiner also notes that with regard to the use limitations in the claim, said use limitations are of no value in a composition claim.

Applicant respectfully traverses the rejection and presents the following comments. It is suggested that kit claims 12-19 are properly defined as articles of manufacture, and not composition claims because they comprise (a) printed instructions for administering temozolomide to a patient and (b) a supply of temozolomide in dosage units. (See as an example, In re Venezia, 189 USPQ 149 (C.C.P.A. 1976), wherein a kit was determined to be an article of manufacture). CA 2,184,545 teaches a capsule containing 5 mg of temozolomide. However, there is no

teaching in CA'545 that teaches the limitation of applicant's instructions. Applicant's instructions require a dosing of TMZ for at least two cycles, wherein each cycle comprises a dosing period of at least five days, at a dose level of 40 to 150 $mg/m^2/day$, followed by a rest period of 5 to 14 days in which TMZ is not administered. Applicant respectfully suggests that there is no motivation in CA'545 to suggest applicant's rest period of 5 to 14 days or cyclical dosing period of 5 to 25 days. In fact, page 5 of the CA'545 patent teaches away from claim 12's rest period where it discloses "a period of about 28 to 42 days, or about 28 to 35 days, or more preferably 28 days, from the first day of temozolomide administration, another administration cycle may be performed. . . ." Applicant respectfully submits that claims 12-19 are not obvious over CA '545.

Reconsideration and withdrawal of this ground of rejection is urged.

In view of the foregoing, applicant submits that the application, as amended, is in condition for allowance and courteously solicits a Notice of Allowance.

The Examiner is requested to call the undersigned attorney on any matter connected with this application.

Respectfully submitted,

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